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Original Article

Diagnostic accuracy of salivary creatinine, urea, and potassium levels to assess dialysis need in renal failure patients

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ABSTRACT

Background: The prevalence of chronic renal failure is increasing because of increase in chronic debilitating diseases and progressing age of population. These patients experience accumulation of metabolic byproducts and electrolyte imbalance, which has harmful effects on their health. Timely hemodialysis at regular intervals is a life-saving procedure for these patients. Salivary diagnostics is increasingly used as an alternative to the traditional methods. Thus, the aim of the present study was to determine the diagnostic efficacy of saliva in chronic renal failure patients.

Materials and Methods: This case–control study included 82 individuals, of which 41 were chronic renal failure patients and 41 were age- and sex-matched controls. Blood and saliva were collected and centrifuged. Serum and supernatant saliva were used for biochemical analysis. Serum and salivary urea, creatinine, sodium, potassium, calcium, and phosphorus were evaluated and correlated in chronic renal failure patients using unpaired *t*-test, Pearson's correlation coefficient, diagnostic validity tests, and receiver operative curve.

Results: When compared to serum; salivary urea, creatinine, sodium, and potassium showed diagnostic accuracy of 93%, 91%, 73%, and 89%, respectively, based on the findings of study.

Conclusion: It can be concluded that salivary investigation is a dependable, noninvasive, noninfectious, simple, and quick method for screening the mineral and metabolite values of high-risk patients and monitoring the renal failure patients.

Key Words: Creatinine, dialysis, renal insufficiency, saliva, serum, urea

INTRODUCTION

Renal diseases contribute a major component to morbidity and mortality;[1] with a prevalence of 17.2%. It has become a global problem necessitating early detection, evaluation, and preventive management to delay progression and to prevent adverse outcomes. Over 1 million people live on dialysis worldwide. The incidence of renal failure has doubled in the last 15 years.[2]

With progressive renal failure, glomerular filtration rate reduces below 15 ml/min leading to accumulation of metabolic byproducts such as urea and creatinine along with imbalance of electrolytes in serum. This necessitates renal replacement therapy (RRT) to avoid the serious complications leading to death. Alternate to RRT, constant timely hemodialysis at regular intervals can be

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life-sustaining tool for these chronic renal failure patients.[3]

Frequency of dialysis or time to initiate dialysis remains the key factor for maintaining homeostasis and to improve the quality of life of these patients. Constant monitoring of serum levels of metabolic byproducts such as creatinine, urea, and potassium is needed. Repeated venipuncture increases patient's infection risks.[4]

Saliva is considered as a filtrate of the blood where various molecules pass through transcellular (passive intracellular diffusion and active transport) or paracellular routes (extracellular ultrafiltration) into saliva. As a result, saliva is equivalent to serum, thereby reflecting the physiological state of the body.[5]

Studies have shown variations in salivary levels of urea, creatinine, sodium, and potassium in renal failure patients.[2,6-9] Based on the availability of improved salivary diagnostic systems, this study was designed to test the diagnostic accuracy of salivary levels of creatinine, urea, sodium, potassium, and calcium using diagnostic validity test, receiver operator characteristic (ROC) curve, and we also aimed to determine cutoff values for salivary creatinine, urea, sodium, potassium, and calcium as indicators of dialysis need in patients with renal failure.

MATERIALS AND METHODS

The study group consisted of 41 recently diagnosed renal failure patients undergoing dialysis for the first time while 41 healthy age- and sex-matched individuals constituted the control group. Written informed consent was obtained from all participants, and detailed clinical history was recorded. Individuals with other diseases, medications, and habits that affect water and electrolyte balance were excluded from the study.

Under aseptic conditions, 2 ml of venous blood was collected from all participants. The samples were centrifuged at 2000 revolutions/min (rpm) for 2–3 min to obtain serum.[3]

All participants were instructed to avoid eating or drinking for 2 h before collection of saliva. Saliva was collected by spitting method after 5 min of relaxation. After collecting, the samples were immediately transferred to a vaccine carrier with ice pack to avoid biochemical changes and carried to the laboratory. The samples were centrifuged at 4000 rpm for 10 min to obtain supernatant saliva. In renal failure patients, blood and saliva were collected 2 h before the dialysis between 9 am and 11 am.

Urea, creatinine, sodium, potassium, calcium, and phosphorus levels were determined in serum and supernatant saliva using semi-autoanalyzer.[3]

Statistical analysis

Comparison of levels of serum and salivary urea, creatinine, sodium, potassium, calcium, and phosphorus between renal failure cases and age- and sex-matched healthy controls was done using unpaired *t*-test. Pearson's correlation coefficient was used to measure the degree of relationship between salivary and serum parameters. Pearson's correlation coefficient has been represented as *r* value, which signifies the extent of linear relationship between two variables (serum and salivary parameters). This statistic varies from − 1 to + 1 going through zero. Any value between –1 and 0 indicates negative correlation and between 0 and + 1 indicates positive correlation. −1 indicates perfect negative linear relationship, +1 indicates perfect positive linear relationship, and 0 indicates two variables are independent of each other.[10] Diagnostic values of salivary parameters were assessed using diagnostic validity tests and were confirmed using ROC curve.

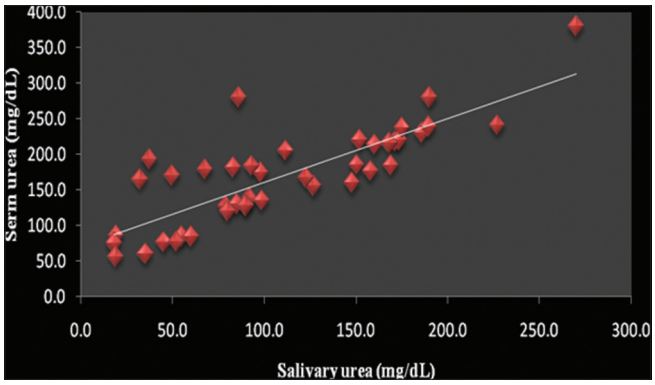
RESULTS

Salivary and serum urea and creatinine

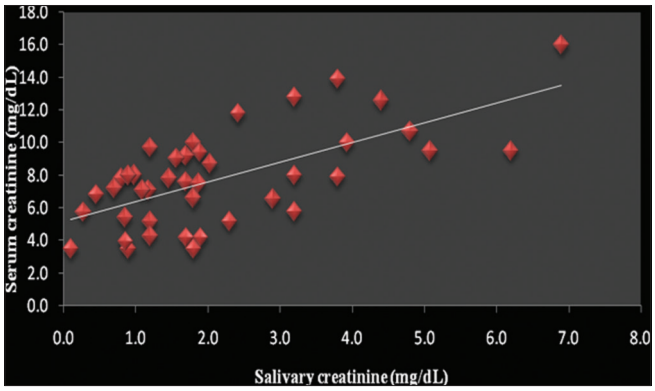
The values of urea and creatinine were significantly high in serum and saliva of cases when compared to controls. A statistically significant positive correlation was detected between serum and salivary urea concentration [r = +0.81, Graph 1, P = 0.00] and between serum and salivary creatinine concentration [r = +0.65, Graph 2, P = 0.00, Table 1]. Salivary urea and creatinine showed diagnostic accuracy of 93% and 91%, respectively. Area under the curve in ROC for salivary urea [Graph 3a] and creatinine [Graph 3b] was 0.9, suggestive of excellent diagnostic accuracy [Table 2].

Salivary and serum sodium levels

The sodium levels were increased significantly with cases both in serum and saliva compared to controls. A statistically significant positive correlation was detected between serum and salivary sodium concentration [r = +0.74, P = 0.00, Table 1]. Diagnostic accuracy and area under curve in ROC for salivary sodium were 73% and 0.7, respectively, suggestive of good diagnostic accuracy [Table 2].



Graph 1: The relationship between salivary and serum urea.



Graph 2: The relationship between salivary and serum creatinine.

Table 1: Correlation of serum and salivary parameters in cases and controls

Correlation between serum and salivary parameters	Cases		Controls	
	r	*P*	*r*	*P*
Urea	+0.81	0.00*	+0.39	0.013*
Creatinine	+0.65	0.00*	+0.313	0.049*
Sodium	+0.74	0.00*	+0.402	0.009*
Potassium	−0.03	0.88 (NS)	+0.286	0.073 (NS)
Calcium	+0.29	0.06 (NS)	−0.009	0.957 (NS)
Phosphorus	+0.271	0.09 (NS)	−0.011	0.065 (NS)

*Statistically significant. *r*: Correlation coefficient; NS: Nonsignificant

Salivary and serum potassium levels

The serum and salivary potassium values were increased significantly with cases compared to controls. A slightly negative correlation was detected between serum and salivary potassium concentration [$r = -0.03$, $P = 0.88$, Table 1]. Diagnostic accuracy of salivary potassium was 89% and area under the curve in ROC was 0.9, suggestive of excellent diagnostic accuracy [Table 2].

Salivary and serum calcium and phosphorus levels

The values of serum and salivary calcium showed slight reduction in cases when compared to controls. The values of serum and salivary phosphorus showed slight increase in cases compared to controls. Correlation between serum and salivary calcium ($r = +0.29$, $P = 0.06$) and between serum and salivary phosphorus [$r = +0.271$, $P = 0.09$, Table 1] was not statistically significant. Hence, cutoff value and diagnostic validity tests were not applicable.

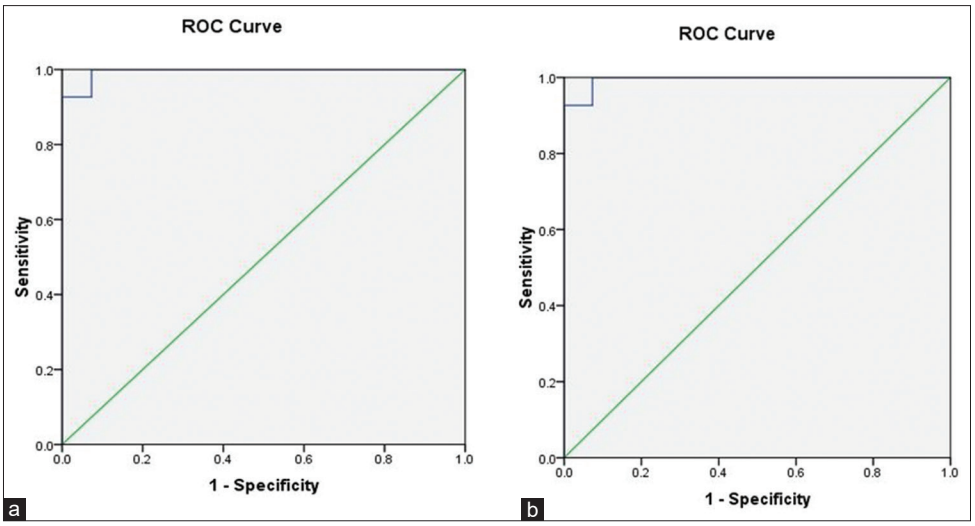
The achieved diagnostic accuracy of salivary urea, creatinine, sodium, and potassium in this study proved that saliva can be used as noninvasive diagnostic fluid in renal failure patients to monitor the levels of above-mentioned parameters. Salivary levels of urea, creatinine, sodium, and potassium were proportional with their serum counterparts, and the mean values of the same are discussed in Table 3.

Cutoff values of the salivary levels of individual parameters were also evaluated. The cutoff values were evaluated in comparison with serum levels, which means any value of a parameter above the cutoff value would be considered as abnormal. Cutoff values obtained in our study are discussed in Table 3.

DISCUSSION

Kidneys regulate the volume and composition of the extracellular fluid to maintain homeostasis by constantly processing the plasma by filtration, reabsorption, and secretion of substances, thereby help in preserving the internal environment of the body.[11] Renal damage reduces glomerular filtration capacity of kidneys and leads to increased serum levels of metabolic byproducts. Among the byproducts, urea and creatinine are important indicators of renal function alterations.[12]

Dialysis is used to remove excess metabolic byproducts in cases of renal failure. During renal failure, continuous monitoring of serum levels of metabolic byproducts decides the need for dialysis. Among all the metabolic byproducts, urea, creatinine, and potassium levels have been considered to be decisive indicators for initiation of dialysis.[4] Considering the disadvantages of invasive serum collection method and ease of saliva collection, saliva is a filtrate of serum and has been explored as an alternative to serum.[13,14] In this study, we examined the use of saliva as an alternative to monitor the metabolic byproducts of kidney failure.



Graph 3: (a) Receiver operating characteristic curve for salivary urea, (b) receiver operating characteristic curve for salivary creatinine. ROC curve: Receiver operating characteristic curve.

Table 2: Combined table of diagnostic validity tests for all the variables

Diagnostic validity tests	Salivary urea versus serum urea	Salivary creatinine versus serum creatinine	Salivary sodium versus serum sodium	Salivary potassium versus serum potassium
Sensitivity (%)	93	93	73	83
Specificity (%)	93	90	73	78
PPV (%)	93	90	73	79
NPV (%)	93	93	73	82
Diagnostic accuracy (%)	93	91	73	89
ROC	0.9	0.9	0.7	0.9

ROC: Receiver operator characteristic curve; PPV: Positive predictive value; NPV: Negative predictive value

Table 3: Mean values and cutoff values of serum and salivary urea, creatinine, sodium, potassium, calcium, and phosphorus

Parameters	Cases		Controls		Cut-off levels	
	Serum	Saliva	Serum	Saliva	Serum	Saliva
Urea (mg/dl)	170.14±67.98	110.05±61.79	25.31±4.55	12.92±4.78	10-50	22
Creatinine (mg/dl)	7.84±2.93	2.20±1.59	0.93±0.13	0.51±0.93	0.5-2	0.69
Sodium (mmol/dl)	163.00±21.17	158.03±47.70	140.87±9.52	127.57±13.68	135-150	133
Potassium (mmol/dl)	5.84±1.86	22.95±8.49	4.47±0.56	8.74±4.43	3.5-5	13
Calcium (mg/dl)	8.29±2.92	8.04±4.67	8.79±0.55	12.09±4.67	Not applicable	
Phosphorus (mg/dl)	15.13±7.76	6.62±2.06	4.35±0.55	3.62±2.94		

Sialometric parameters vary with age and sex. After reaching maximum development at the age of 15 years,[15] salivary gland parenchyma will be gradually replaced by adipose and fibrovascular tissue leading to reduction in volume of acini in turn leading to sialometric alterations.[16] In addition, women present smaller salivary glands in comparison with men; this along with female hormonal pattern may contribute to variation in salivary parameters among the sexes.[16] Considering the above factors, age- and sex-matched controls were used for comparison in the study.

Salivary urea[6-9,17] and creatinine[18,19] levels showed positive correlation with serum levels both in cases and controls. This finding is in accordance with the previous finding.[3,6-9,17-22]

The correlation of salivary urea and creatinine level so with serum further saliva as an ultra-filtrate of serum.[23] In this study, variations in serum urea and creatinine levels corresponded to variations in salivary levels. However, the rate of change was not constant.

The correlation coefficient of salivary and serum urea level was 0.8 while that of salivary and serum

creatinine was 0.69. Similar results were obtained by other studies.[18,19] Although no previous explanation is available for this finding, the cause may be the lower molecular weight and size of urea at 60.03 D and 0.26 nm,[23,24] respectively, in comparison with that of creatinine at 113 D and 0.3 nm,[25] leading to a greater filtration of urea in comparison to creatinine.

A significant positive correlation was found between salivary sodium level and serum sodium level, whereas slight negative correlation was obtained when salivary and serum potassium levels were compared and correlated. The salivary concentration of these ions (sodium and potassium) does not depend entirely on their serum concentration, and instead depend on differing, reabsorption of sodium and secretion of potassium in the striated ducts of salivary glands, thus explaining the increase potassium ion concentration in saliva than in serum.[26] Very high correlation coefficient of $r = +0.5$ was found between serum and salivary potassium in patients undergoing dialysis by Nagler.[27]

Serum and salivary calcium levels did show positive correlation but were statistically not significant. Our findings are in accordance with that of the previous studies.[3,18] The reduction in serum and salivary calcium level is the consequence of a fall in 1,25 dihydroxycholecalciferol, an active metabolite of Vitamin D synthesized in the kidney which plays a main role in calcium absorption from intestine,[4,28] thereby causing dip in the calcium levels in serum and saliva.

Serum and salivary phosphorus values showed statistically nonsignificant increase in the study group and positive correlation was obtained between serum and salivary phosphorus but was statistically nonsignificant. Our finding of increased level of salivary phosphorus was in agreement with a study done by Savica *et al*.[29] The increase in serum and salivary phosphorus levels can be explained by diminished phosphate load in the filtrate. The amount of the phosphate filtered is completely reabsorbed in the tubules, thus increasing plasma level of phosphorus. These increased phosphorus ions forms complex with calcium ions forming calcium phosphate. Hence, hyperphosphatemia is dangerous due to increased risk of precipitation of calcium phosphate in soft tissue and in walls of blood vessels, contributing to cardiovascular calcification in renal failure patients.[28] Hence, increase in the level of salivary phosphorus is due to renal function deterioration.[30]

The salivary urea showed sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of 93% and overall diagnostic accuracy of salivary urea was found to be 93% in this study. This suggested that salivary urea has excellent diagnostic accuracy which was also confirmed by its score of 0.9 of area under the curve in ROC. Similar findings were obtained by other authors.[19,20] However, comparatively, lesser values of sensitivity of 80%, specificity of 71%, PPV of 80%, and NPV of 71% were demonstrated by Zuniga *et al*.,[8] whereas sensitivity of 80%, specificity of 90%, and area under the curve of 0.898 in ROC were demonstrated by Xai *et al*.[6]

The salivary creatinine showed sensitivity of 93%, specificity of 90%, PPV of 90%, NPV of 93%, and overall diagnostic accuracy of 91% which suggested that salivary creatinine has excellent diagnostic accuracy, which was also confirmed by its score of 0.9 of area under the curve in ROC. Parallel findings were obtained by previous studies.[19,20] However, comparatively, less diagnostic accuracy was demonstrated by Xai *et al*.,[6] in which sensitivity was 77%, specificity was 98%, and area under the curve was 0.897 in ROC.

Minor disparity in the diagnostic accuracy of urea and creatinine between studies could be due to difference in sample size, method of estimation, time and method of sample collection.

The salivary sodium showed sensitivity, specificity, PPV, NPV of 73% and overall diagnostic accuracy of 73%, which suggested that salivary sodium had good diagnostic accuracy and was confirmed by its score of 0.7 of area under the curve in ROC. The salivary potassium showed sensitivity of 83%, specificity of 78%, PPV of 79%, NPV of 82% with overall diagnostic accuracy of 89% which suggested that salivary potassium had excellent diagnostic accuracy confirmed by its score of 0.9 of area under the curve in ROC.

CONCLUSION

Based on the findings of this study, we concluded that salivary diagnostics is a simple, quick, noninvasive, inexpensive, highly accurate, and reliable technique to assess the serum levels of metabolic byproducts and electrolytes in patients with renal failure. The

salivary urea, creatinine, sodium, and potassium are diagnostically accurate and can be used to monitor serum levels of metabolic byproducts such as urea and creatinine and for screening of high-risk patients to assess the need for dialysis.

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Conflicts of interest

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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